IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Michael KRETSCHMAR et al.	:	**Confirmation No.:** 1342
Serial No.: 10/594,453	:	**Group Art Unit:** 1656
Filed: September 26, 2006	:	**Examiner:** Marsha M. TSAY

For: A PROCESS FOR REMOVING FIBRONECTIN FROM PLASMA FRACTIONS

Attorney Docket No.: LNK-019

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Commissioner for Patents
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

Applicants hereby request that a panel of examiners be convened to formally review the legal and factual basis of the rejections in the instant application in accordance with the procedures outlined in the OG Notice of July 12, 2005. Applicants respectfully submit that the **Final Rejection of April 26, 2010** is fundamentally flawed, lacking both legal and scientific foundation. Further to this position, Applicants submit the enclosed remarks (no longer than 5 pages) and respectfully petitions for reconsideration of the outstanding grounds of rejection in view of the arguments therein. Applicants further petition for the summary issuance of a notice of allowance in view of the following remarks:

REMARKS

Claims 2, 4-8, 10-15, 17, and 24 are presently pending and provided herewith as Appendix A. Claims 2, 4-8, 10-15, 17, and 24 stand finally rejected on prior art grounds of record as follows:

- Claims 2, 4-8, 10-14 and 24 stand rejected under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (U.S Patent No. 4,341,764, previously cited) in view of Newman et al. (U.S. Patent No. 5,710,254, previously cited); and
- Claims 15 and 17 stand rejected under 35 U.S.C. § 103(a) as being obvious over Wallace and Newman, further in view of Burnouf-Radosevich et al. (U.S. Patent No. 5,408,039, previously cited).

Applicants respectfully submit that these rejections hinge on an improper characterization of the Wallace reference and an improper application of the obviousness standard. Applicant's position on the proper interpretation of Wallace reference is set forth at length in the responses of October 27, 2008 (p. 10-12), July 9, 2009 (p. 4-5) and January 4, 2010 (p. 6-8) and summarized hereinbelow:

1. **Neither Wallace nor Newman disclose or suggest a plasma fraction containing "NaCl or KCl at a concentration of 100 to 200 mM".**

While *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 USPQ2d 1385 (2007) may indeed prescribe a more relaxed approach to the obviousness analysis, it nevertheless maintains the requirement that the prior art references when combined teach or suggest all the claim limitations. Thus, a proper post-KSR obviousness determination still requires the Office make "a searching comparison of the claimed invention – including all its limitations – with the teachings of the prior art." *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) and *CFMT v. Yieldup Intern. Corp.*, 349 F. 3d 1333, 1342 (Fed. Cir. 2003).

In this case, the Examiner cites to Newman to cure the failure of Wallace to teach an initial concentration of NaCl. However, as the Examiner herself admits, Newman describes an initial concentration of only "**40 mM NaCl**". See FOA, p. 4, and Newman, 2: 22-24. The Examiner then asserts that "it would be reasonable for one of ordinary skill to determine at [sic]

which concentration of NaCl can be added to an initial preparation of cryoprecipitate to preserve the activity of the blood factors that one of ordinary skill would like to purify". See FOA, p. 10.

Applicants respectfully submit that the Examiner's open-ended application of the "obvious to try" standard has been expressly rejected by the court in *In Re Kubin*, 561 F. 3d 1351 (Fed. Cir. 2009). In particular, the *Kubin* court stated that the "obvious to try" standard under § 103(a) may not be applied where one would have "to vary all parameters … where the prior art gave either no indication of which parameters were critical …" or "where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." Given the silence of the prior art teachings and the fact that overly high salt concentrations are known to result in the inadvertent precipitation of a desired product (see Applicants' specification at page 3), Applicants respectfully submit that the Examiner's assertion that it would have been "obvious" to utilize a salt concentration that is, at a minimum, 150% higher than that disclosed by the prior art (Newman) is *per se* improper and cannot be maintained.

2. Wallace does not suggest the combination of a process temperature of 20 to 25 °C and a process pH of 4.7 to 5.3 as a means to deliver a precipitate comprising 70 to 99% of the initial amount of fibronectin.

The Examiner asserts that since Wallace generally discloses a temperature range of 2 to 20 °C and a pH range of 5.0 to 6.95, practicing the method of Wallace at a temperature of 20 °C and a pH of 5.0 to yield greater than 60% fibronectin recovery is expressly taught by the reference. Applicants respectfully disagree. As noted previously, Wallace emphasizes the use of a chilling step to maximize fibronectin recovery. Specifically, Wallace discloses a pH range of 5.0 to 6.95, more preferably about 6.5 to 6.95, using a solution chilled to a temperature of about 2°- 20° C, preferably about 2.5°- 7.5°C (col. 2: 37-40, emphasis added). Wallace later suggests that the disclosed processes may be used to obtain a yield of "greater than 50%", preferably "greater than 60%" of the fibronectin (col. 4: 41-42). One of skill in the art, in considering these two sections together, would readily expect that only use of the more preferred conditions (i.e., pH of 6.5 to 6.95 and temperature of 2.5°- 7.5°C) would give rise to the more preferred yield (i.e., "greater than 60%"). Likewise, the skilled artisan would expect that any deviation from these preferred conditions (e.g., pH of 5.3 and less and temperature of 20°C and higher as

presently claimed) would give rise to a lesser yield (i.e., less than 60%, more likely less than 50%). Accordingly, Applicants respectfully submit that the presently claimed process, including a process temperature of 20°C to 25 °C, a process pH of 4.7 to pH 5.3, and a fibronectin yield of 70% to 99%, cannot be fairly characterized as obvious in view of the Wallace disclosure.

Furthermore, it is apparent from a comparison of Wallace's Figures 1 and 2 that only the preferred parameters (pH of 6.5 to 6.95 and temperature of 2.5°- 7.5°C) permit single step removal (Figure 1: an acid-chill precipitate process). Conversely, if one utilizes a lower pH (i.e., a pH 5.0 to 6.8, more preferably 5.8 to 6.4) and omits the chilling step, a distinct two-step procedure such as that shown in Figure 2 is required to remove fibronectin (step one: acid precipitate, step two: chill precipitate). Wallace's accompanying specification suggests that a chill precipitate such as produced by the process of Figure 2 has substantially more fibronectin-like activity than either the acid-chill precipitate of Figure 1 or the acid-precipitate of Figure 2 (col. 3, lines 28-30). This confirms Applicants' position that Wallace suggests (a) towards a two-step process and (b) away from a one-step acid-precipitate process such as that presently claimed. Taken together, this gives rise to an expectation that the process as presently claimed would be less effective, providing a yield of less than the preferred 60% and more likely less than 50% -- certainly well below the 70% to 99% fibronectin recovery required by the pending claims.

3. The unexpected superior results associated with the process of the instant invention serve as clear indicia of non-obviousness.

It is well settled that even a *prima facie* case of obviousness may be rebutted by so-called "indicia of non-obviousness", e.g., evidence that a claimed invention yields unexpectedly improved properties or properties not present in the prior art and/or evidence that the claimed invention possesses unexpected properties. See *In re Dillon*, 919 F.2d 688 at 692-93, 16 USPQ2d 1901 (Fed. Cir. 1990); *In re Albrecht*, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975). Herein, the Examiner rejected Applicants' assertion of criticality and unexpected results, citing to *In re Aller* for the position that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation". See FOA, p. 9.

Applicants respectfully submit that the Examiner's reliance of *Aller* is misplaced. In *Aller*, the court held that one of ordinary skill would have expected a reaction rate to be slowed at a known rate by a reduction in temperature and accelerated at a known rate by an increase in acid concentration. Thus, the claim of superior results arising from lower temperature and higher acid parameters was dismissed as insufficiently unexpected (i.e., if the prior art recognizes the known effect attributed to a claimed parameter, then it is logical to conclude that changes to that parameter produce only expected results). However, the instant situation is exactly opposite to that of *Aller*. Specifically, Wallace suggests a preference for lower temperatures and higher pHs. Thus, one would expect higher temperatures and lower pH values to give rise to a reduced yield and accordingly would indeed be surprised by fibronectin yields on the order of 70% to 99% as required by the pending claims. In other words, since the predicted means for optimizing results is exactly inapposite to the direction taken by Applicants, the presently claimed invention cannot be fairly characterized as "obvious" from the prior art teachings.

CONCLUSION

Thus, it is readily apparent that the Final Rejection of April 26, 2010 contains fundamental and clear errors and untenable positions that cannot withstand the scrutiny of appeal. For this reason, it should be withdrawn.

Respectfully submitted,

Date: **July 26, 2010**

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APPENDIX A: CLAIMS AT ISSUE

1. (Canceled).
2. (Previously Presented) A process for the production of a composition containing at least one coagulation factor, said process consisting of the following steps:
   i. adjusting the pH of a plasma fraction, wherein said plasma fraction contains an initial amount of fibronectin and at least one coagulation factor, contains NaCl or KCl at a concentration of 100 – 200 mM and is characterized by an ionic strength below 500 mM, to a value between pH 4.7 and pH 5.3 so as to form a precipitate comprising 70% to 99% of the initial amount of fibronectin and a supernatant containing said at least one coagulation factor,
   ii. removing the fibronectin precipitate formed in step (i) to thereby yield a composition containing at least one coagulation factor; and
   iii. treating the composition obtained in step (ii) to yield at least one purified coagulation factor,

   wherein steps (i) and (ii) are performed at a temperature that ranges from 20°C to 25 °C.
3. (Canceled)
4. (Previously Presented) The process according to claim 2, characterized in that the ionic strength of the plasma fraction is below 300 mM.
5. (Previously Presented) The process according to claim 2, characterized in that the ionic strength of the plasma fraction is below 200 mM.
6. (Previously Presented) The process according to claim 2, wherein removing step (ii) consists of stirring the plasma fraction for at least 10 minutes.
7. (Previously Presented) The process according to claim 2, characterized in that the majority of the fibronectin precipitate is separated by means of an agitator blade of a stirrer.
8. (Previously Presented) The process according to claim 2, characterized in that the plasma fraction initially contains fibronectin at a concentration of at least 0.1 g per liter.

9. (Canceled)
10. (Previously Presented) The process according to claim 2, characterized in that the plasma fraction initially contains glycine at a concentration below 500 mM.
11. (Previously Presented) The process according to claim 2, characterized in that the plasma fraction initially contains glycine at a concentration below 200 mM.
12. (Previously Presented) The process according to claim 2, characterized in that the plasma fraction initially contains glycine at a concentration of 50 to 200 mM.
13. (Previously Presented) The process according to claim 2, characterized in that the plasma fraction initially contains glycine at a concentration of 100 to 150 mM.
14. (Previously Presented) The process according to claim 2, characterized in that the plasma fraction is dissolved cryoprecipitate.
15. (Previously Presented) The process according to claim 14, characterized in that the dissolved cryoprecipitate is previously purified by (a) treatment with aluminum hydroxide, (b) treatment with a solvent and/or a detergent, and (c) anion exchange chromatography.
16. (Canceled)
17. (Previously Presented) The process according to claim 2, characterized in that the at least one coagulation factor is von Willebrand factor.
18. (Canceled)
19. (Canceled)
20. (Canceled)
21. (Canceled)
22. (Canceled)
23. (Canceled)
24. (Previously Presented) The process according to claim 2 , wherein the fibronectin precipitate obtained in step (i) contains at least 90% of the initial amount of fibronectin.